201-14852A

HIGH PRODUCTION VOLUME (HPV) CHALLENGE PROGRAM

TEST PLAN
FOR
DIMETHYL 1,4-CYCLOHEXANEDICARBOXYLATE
(CAS NO.: 94-60-0)

PREPARED BY:

EASTMAN CHEMICAL COMPANY

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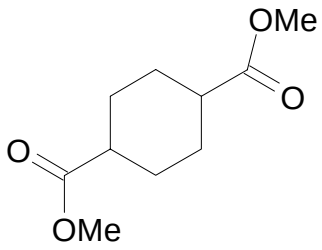
OVERVIEW

The Eastman Chemical Company hereby submit for review and public comment the test plan for dimethyl-1,4-cyclohexanedicarboxylate (DMCD; CAS No.: 94-60-0) under the Environmental Protection Agency's (EPA) High Production Volume (HPV) Chemical Challenge Program. The chemical represented by this CAS number consist of a mixture of both *cis*- and *trans*- isomers. In preparing this test plan, Eastman has given careful consideration to the principles contained in the letter the EPA sent to all HPV Challenge Program participants on October 14, 1999. As directed by EPA in that letter, we have sought to maximize the use of existing data for scientifically appropriate related chemicals and structure-activity-relationships. Additionally, and also as directed in EPA's letter, in analyzing the adequacy of existing data, Eastman has conducted a thoughtful, qualitative analysis rather than use a rote checklist approach.

It is the intent of our company to adequately fulfill all endpoints in the Screening Information Data Set for the physicochemical, environmental fate, ecotoxicity test, and human health effects endpoints. This will be accomplished using existing data on DMCD (CAS No.: 94-60-0), DMCD as a pure *trans*- isomer (CAS No.: 3399-22-2), or with data on a structural analog, 1,4-Cyclohexanedicarboxylic acid (CAS No.: 1076-97-7). In addition, EPA-acceptable predictive computer models and values from reputable textbooks are used to fulfill various endpoints. We believe that, in total, these data are adequate to fulfill all the requirements of the HPV program without need for the conduct any new or additional tests.

DMCD is a colorless partially crystallized liquid capable of being manufactured to a high degree of purity. The primary use for this compound is as an industrial intermediate in the manufacture of various types of polymers and resins. Accordingly, as an industrial intermediate used in the synthesis of polymers, exposure to the environment and general public is essentially non-existent. DMCD, as supplied by Eastman Chemical Company, is lawful for use as a monomer for polyesters used as a component of food packaging adhesive under the conditions defined in regulations administered by the U. S. Food and Drug Administration at 21 CFR 175.105.

TEST PLAN SUMMARY

CAS No. 94-60-0 	Information	OECD Study	Other	Estimation	GLP	Acceptable	New Testing Required
STUDY	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N
PHYSICAL-CHEMICAL DATA							
Melting Point	Y	-	Y	Y	N	Y	N
Boiling Point	Y	-	Y	-	N	Y	N
Vapor Pressure	Y	-	Y	Y	N	Y	N
Partition Coefficient	Y	-	Y	Y	N	Y	N
Water Solubility	Y	-	Y	Y	N	Y	N
ENVIRONMENTAL FATE ENDPOINTS							
Photodegradation	Y	-	-	Y	N	Y	N
Stability in Water	Y	-	-	Y	N	Y	N
Biodegradation	Y[1]	Y	-	-	Y	Y	N
Transport between Environmental Compartments (Fugacity)	Y	-	-	Y	N	Y	N
ECOTOXICITY							
Acute Toxicity to Fish	Y[1]	-	Y	-	N	Y	N
Acute Toxicity to Aquatic Invertebrates	Y[1]	-	Y	-	N	Y	N
Toxicity to Aquatic Plants	Y	Y	-	-	Y	Y	N
TOXICOLOGICAL DATA							
Acute Toxicity	Y	Y	-	-	Y	Y	N
Repeated Dose Toxicity	Y[2]	Y	-	-	Y	Y	N
Genetic Toxicity – Mutation	Y[2]	-	Y	-	Y	Y	N
Genetic Toxicity – Chromosomal Aberrations	Y[2]	-	Y	-	Y	Y	N
Developmental Toxicity	Y	Y	-	-	Y	Y	N
Toxicity to Reproduction	Y	Y	-	-	Y	Y	N

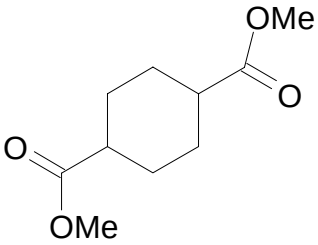
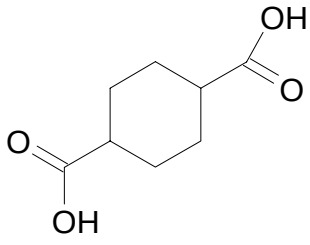
1. Study was conducted using the *trans* isomer of DMCD (CAS No.: 3399-22-2).
2. Endpoint was completed using 1,4-Cyclohexanedicarboxylic acid (CAS No.: 1076-97-7) as a surrogate.

JUSTIFICATION FOR USE OF DATA FROM A CHEMICAL ANALOG

As a means to reduce the number of tests that may be conducted, the EPA allows for the use of categories to group together chemicals that are structurally similar to characterize specific SIDS endpoints (USEPA 1999). Accordingly, the SIDS endpoints evaluating the potential for DMCD to induce genotoxicity (mutations and aberrations) and systemic toxicity followed repeated exposure was completed through the use of a structurally similar chemical that is believed to be a metabolite of DMCD. The analog chemical used for some endpoints was 1,4-cyclohexanedicarboxylic acid (CHDA; CAS No.: 1076-97-7). It is fully anticipated in biological systems that of the methyl units attached to the carboxyl side chains of DMCD will undergo enzymatic cleavage to yield CHDA. While there are no data definitively demonstrating this cleavage for this particular compound, there are data that demonstrate the body's ability to cleave short to medium length alkyl chain esters located in the one and four positions on similar compounds. Specifically, the methyl units of 1,4-benzenedicarboxylic acid, dimethyl ester (dimethylterephthalate; DMT) and the ethylhexyl moieties of 1,4-benzenedicarboxylic acid, bis(2-ethylhexyl) ester are readily removed to form 1,4-benzenedicarboxylic acid (terephthalic acid; TPA) (Barber et al., 1994 and Heck and Tyl, 1985). In addition, data exist on the cleavage of ester bonds with numerous other ester compounds

synthesized by joining short chain alcohols and acids (eg. methyl-, ethyl-, and butyl-acetate) and various glycol ethers that have been acetylated.

From a toxicological perspective neither DMCD nor its analog acid exhibited any toxicity following repeated dietary exposures at a level of 1%. The duration of exposure was only 12 days for DMCD while it was 28 days for CHDA. Both compounds do not appear to be acutely toxic, although the methyl ester compound appears to be less toxic to males.

		
Chemical	1,4-Cyclohexanedicarboxylic acid, dimethyl ester	1,4-Cyclohexanedicarboxylic acid
CAS No.	94-60-0	1076-97-7
Acute Toxicity (LD_{50})	>5,000 mg/kg (males) Approx. 2812 mg/kg (females)	1,903 mg/kg (males)[1] 2,263 mg/kg (females)
Repeat Dose Toxicity	No effects were noted following a 12-day dietary exposure at a level of 1%.	No effects were noted following a 28-day dietary exposure at a level of 1%.[2]

1. Unpublished study Eastman Chemical Company; HAEL 83-0158, February 23, 1995
2. Unpublished study Eastman Kodak Company; HAEL 87-0082, January 8, 1988

TEST PLAN DESCRIPTION FOR EACH SIDS ENDPOINT

A. Physicochemical

Melting point - A value for this endpoint was obtained using MPBPWIN v1.40, a computer estimation model in EPIWIN (1).

Boiling Point - A value for this endpoint was obtained from a reputable textbook referenced in HSDB.

Vapor Pressure - A value for this endpoint was obtained using MPBPWIN v1.40, a computer estimation model in EPIWIN.

Partition Coefficient - A value for this endpoint was obtained using KOWIN v1.66, a computer estimation model in EPIWIN.

Water Solubility - A value for this endpoint was obtained using WSKOWIN v1.40, a computer estimation model in EPIWIN.

Conclusion: All end points haven been satisfied by the utilization of data obtained from the various physical chemical data modeling programs within the EPIWIN suite or have been satisfied by the utilization of data obtained from various textbooks referenced within the HSDB (1). The results from the utilization of the models within EPIWIN have been noted by the Agency as acceptable in lieu of actual data or values identified from textbooks (2). No new testing is required.

B. Environmental Fate

Photodegradation - A value for this endpoint was obtained using AOP v1.90, a computer estimation model in EPIWIN.

Stability in Water - A value for this endpoint was obtained using HYDROWIN v1.67, a computer estimation model in EPIWIN.

Biodegradation - This endpoint was satisfied through data derived from a study on the *trans*- isomer of DMCD (CAS No.: 3399-22-2). The study followed OECD test guideline 301-B and was conducted under GLP assurances. However, the chemical assessed was

Fugacity - A value for this endpoint was obtained using the EQC Level III partitioning computer estimation model found within EPIWIN.

Conclusion: All endpoints have been satisfied using actual data or through the utilization of Agency-acceptable estimation models. In total they are of sufficient quality to conclude that no additional testing is needed.

C. Ecotoxicity Data

Acute Toxicity to Fish - This endpoint was satisfied through data derived from a study on the *trans*- isomer of DMCD (CAS No.: 3399-22-2). The study followed established EPA guidelines (600/3-75-009 and 600/4-85/013, 3rd Ed.) but was not conducted under GLP assurances. The study quality was deemed to be "reliable with restrictions".

Acute Toxicity to Aquatic Invertebrates - This endpoint was satisfied through data derived from a study on the *trans*- isomer of DMCD (CAS No.: 3399-22-2). The study followed established EPA guidelines (600/3-75-009 and 600/4-85/013, 3rd Ed.) but was not conducted under GLP assurances. The study quality was deemed to be "reliable with restrictions".

Toxicity to Aquatic Plants - This endpoint is filled by data from an OECD TG-201 study conducted under GLP assurances. The quality of this study was deemed "reliable without restrictions".

Conclusion: All endpoints have been satisfied with data from well-conducted studies following established guidelines. The data from the fish and Daphnia studies were conducted on the pure *trans* isomer while the algae were exposed to both isomers. In total they are of sufficient quality to conclude that no additional testing is needed.

D. Toxicological Data

Acute Toxicity - This endpoint is filled by data from a study that followed OECD test guideline 401 and was conducted under GLP assurances. The quality of this study was deemed "reliable without restrictions".

Repeat Dose Toxicity - This endpoint is filled by data from 28-day dietary intake study that followed OECD guideline 407 and was conducted under GLP assurances. The chemical evaluated in this study was the structural surrogate 1,4-cyclohexanedicarboxylic acid (CHDA; CAS No.: 1076-97-7). The quality of this study was deemed "reliable without restrictions". Data on DMCD are also presented but the study was only 2 weeks in duration.

Genetic Toxicity

Mutation - This endpoint is filled with a single study in *Salmonella typhimurium* (strains TA 98, 100, 1535, and 1537) and *Escherichia coli* (strain WP2*uvr*A). This study followed methods similar to OECD guideline 471 and was conducted under GLP assurances. The chemical evaluated in this study was the structural surrogate 1,4-cyclohexanedicarboxylic acid (CHDA; CAS No.: 1076-97-7). The quality of this study was deemed "reliable without restrictions".

Aberration - This endpoint is filled with data from an *in vitro* study using Chinese hamster ovary (CHO) cells that followed methods similar to OECD guideline 473 and was conducted under GLP assurances. The chemical evaluated in this study was the structural surrogate

	1,4-cyclohexanedicarboxylic acid (CHDA; CAS No.: 1076-97-7). The quality of this study was deemed "reliable without restrictions".
Developmental Toxicity -	This endpoint is filled by data from a dietary exposure study in rats that followed OECD test guideline 421, and was conducted under GLP assurances. This protocol evaluates both developmental and reproductive toxicity potential. The quality of this study was deemed "reliable without restrictions".
Reproductive Toxicity -	This endpoint is filled by data from a dietary exposure study in rats that followed OECD test guideline 421, and was conducted under GLP assurances. This protocol evaluates both developmental and reproductive toxicity potential. The quality of this study was deemed "reliable without restrictions".
Conclusion:	All endpoints have been satisfied with data from studies whose methods followed established guidelines, or utilized methods that were very similar and or scientifically appropriate. All studies were conducted under GLP assurances. In total, they are of sufficient quality to conclude that no additional testing is needed.

SIDS DATA SUMMARY

Data assessing the various physicochemical properties (melting point, boiling point, vapor pressure, partition coefficient, and water solubility) for DMCD were either obtained from reputable text references found in the HSDB or were estimated using the models within EPIWIN. These data indicate that DMCD is a liquid at room temperature (MP = -46.41 ^{o}C) with a very low vapor pressure (0.0822 mmHg). It has a relatively low estimated octanol to water partition coefficient (K_{ow} = 2.11) and accordingly is estimated to be only fairly soluble in water (688.7 ppm).

The assessment of the environmental fate endpoints (photodegradation, biodegradation, stability in water, and fugacity) was completed through the use of available data and estimation modeling programs within EPIWIN. As a result of its estimated K_{ow}, solubility in water, and relatively low volatility, fugacity estimations predict that DMCD will distribute primarily to soil and water. As DMCD is an ester its stability in water was assessed using the computer estimation program in EPIWIN. Results of that program predict it to have a half-life of greater than one year. Thus, it should be considered hydrolytically stable and further testing is not required. The biodegradability of DMCD (*trans* isomer; CAS No.: 3399-22-2) was determined by following OECD test guideline 301B. Results of this study demonstrated DMCD would not be readily degraded by wastewater organisms as defined by the time frames specified in the test. However, it was very close and its overall degradation at study termination was such that it would not be predicted to persist in the environment. Computer estimation models also indicate DMCD would be quite susceptible to attack by atmospheric hydroxyl radicals and would be expected to degrade in the atmosphere at a relatively fast rate with an estimated half-life of about 1.35 days. Its primary use as an industrial intermediate in the production of polymers and resins will result in minimal environmental releases.

The potential toxicity of DMCD to fish, Daphnia, and algae were determined through either well-conducted OECD or EPA guideline studies. The results of these studies indicate that fish may be sensitive to DMCD as its LC_{50} was 23 mg/L. DMCD did not appear to be toxic to the other organisms as no effects were noted at the highest concentrations tested (100 and 125 mg/L). Due to its use as an industrial intermediate, the potential for significant exposures to aqueous environments is unlikely accept under accidental conditions.

The potential to induce toxicity in mammalian species is very low. DMCD exhibited an LD_{50} value in rats of greater than 5,000 mg/kg in males and about 2,812 mg/kg in females. Results of an acute toxicity test on a pure *trans*-isomer (CAS No. 3399-22-2) was >3,200 mg/kg for both sexes. Data from a repeat exposure study in rats following OECD guidelines (TG-407) assed the toxicity of CHDA, a structural surrogate, over a 4-week period. In this study, CHDA (CAS No.: 1076-97-7) absolutely no evidence of toxicity was manifested at dietary levels up to 1.0% that resulted in doses of 871 mg/kg (males) and 894 mg/kg (females). Results of this study are identical with a shorter-term repeat dose study conducted on DMCD. In that study, male rats were exposed for 12 days at a maximum level

of 1% (1,000 mg/kg) with no evidence of toxicity. The ability of DMCD to induce chromosomal damage was assessed using the structural surrogate CHDA (CAS No.: 1076-97-7). Results from mutagenicity and chromosomal aberration studies on CHDA (CAS No.: 1076-97-7) indicate this material is not genotoxic. Developmental and reproductive toxicity endpoints were assessed simultaneously through the conduct of a developmental/reproductive toxicity study in rats that followed OECD test guidelines (TG-421). Based on the results of this study, it was concluded that DMCD was not teratogenic and did not show evidence of reproductive toxicity at the highest concentration tested in the diet (1.5%). This dietary level translates to a NOAEL of 888 mg/kg for males and 1,124 mg/kg for females.

In conclusion, the summarized hazard data indicate that this chemical should constitute a low risk to workers and the environment (if accidentally spilled). All endpoints have been completed with data of suitable quality and no new tests are being recommended. Due to its only current known use as an industrial intermediate in the formation of polymers and no known direct applications in consumer products, exposure to the general public is greatly minimized.

EVALUATION OF DATA FOR QUALITY AND ACCEPTABILITY

The collected data were reviewed for quality and acceptability following the general US EPA guidance (3) and the systematic approach described by Klimisch *et al.* (4). These methods include consideration of the reliability, relevance and adequacy of the data in evaluating their usefulness for hazard assessment purposes. This scoring system was only applied to ecotoxicology and human health endpoint studies per EPA recommendation (5). The codification described by Klimisch specifies four categories of reliability for describing data adequacy. These are:

1. Reliable without Restriction: Includes studies or data complying with Good Laboratory Practice (GLP) procedures, or with valid and/or internationally accepted testing guidelines, or in which the test parameters are documented and comparable to these guidelines.

2. Reliable with Restrictions: Includes studies or data in which test parameters are documented but vary slightly from testing guidelines.

3. Not Reliable: Includes studies or data in which there are interferences, or that use non-relevant organisms or exposure routes, or which were carried out using unacceptable methods, or where documentation is insufficient.

4. Not Assignable: Includes studies or data in which insufficient detail is reported to assign a rating, e.g., listed in abstracts or secondary literature.

REFERENCES

1. EPIWIN, Version 3.10, Syracuse Research Corporation, Syracuse, New York.

2. US EPA. (1999). The Use of Structure-Activity Relationships (SAR) in the High Production Volume Chemicals Challenge Program. OPPT, EPA.

3. USEPA (1998). 3.4 Guidance for Meeting the SIDS Requirements (The SIDS Guide). Guidance for the HPV Challenge Program. Dated 11/2/98.

4. Klimisch, H.-J., Andreae, M., and Tillmann, U. (1997). A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data. *Regul. Toxicol. Pharmacol.* 25:1-5.

5. USEPA. 1999. Determining the Adequacy of Existing Data. Guidance for the HPV Challenge Program. Draft dated 2/10/99.

6. Barber ED, Fox JA and Giordano CJ (1994b). Hydrolysis, absorption and metabolism of di(2-ethylhexyl) terephthalate in the rat. Xenobiotica **24**, 441-450.

7. Heck, H. d'A., and Tyl, R.W. (1985) “The Induction of Bladder Stones by Terephthalic Acid, Dimethyl Terephthalate, and Melamine (2,4,6-Triamino-s-triazine) and its Relevance to Risk Assessment” Regul. Toxicol. Pharmacol., 5:294-313.